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# Interphotoreceptor Retinoid-Binding Protein Implications in Diabetic Retinopathy

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## Abstract

The interphotoreceptor retinoid-binding protein (IRBP) is the most abundant protein in the interphotoreceptor matrix (IPM) and its levels decrease beginning in the early stages of diabetes. IRBP participates in the delivery of retinoids between retinal cells to carry out the visual cycle and also protects those retinoids against degradation in the IPM. IRBP deficiency is related to several conditions such as retinitis pigmentosa, cone-rod dystrophy, increased oxidative stress in the photoreceptors, and myopia. Decreased IRBP levels in diabetes could be due to the secretion of inflammatory cytokines and a direct effect of hyperglycemia on the photoreceptors. It is known that prior to the occurrence of vascular changes in diabetic retina, electrophysiological alterations occur on early potentials. Alterations on the photoreceptor outer segments and increased oxidative stress indicate an important affliction of the photoreceptors from early stages. Due to the importance of IRBP in photoreceptor wellness, its decreased levels may be linked to early photoreceptor affection. More studies are required to describe in detail the whole impact that decreased levels of IRBP in diabetes may have.

**Keywords:** interphotoreceptor retinoid-binding protein, IRBP, visual cycle, oxidative stress, ER-stress, light damage, retinitis pigmentosa, cone-rod dystrophy, photoreceptor damage, photoreceptor, S-cones, M-cones, outer segment, diabetes, neurodegeneration

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## 1. Introduction

Typically, the pathological changes described in diabetic retina involve neovascularization and increased blood vessel permeability, a condition known as diabetic retinopathy (DR). Early changes that occur prior to the vascular affection have been acquiring more interest by the scientific community. Retinal proteomic analysis, functional and histopathological studies have revealed alteration in the levels of some proteins and a neurodegeneration state mainly involving ganglion and photoreceptor cells accompanied by reactive gliosis [1–5].

The interphotoreceptor retinoid-binding protein (IRBP), which is the most abundant protein in the interphotoreceptor matrix (IPM) [6–10], is one of the principal elements altered in early stages of diabetes. This protein is expressed mainly by the cone and rod photoreceptor cells [11–13]. It binds to the retinoids in the interphotoreceptor matrix and facilitates their exchange between the IPM and the cells that carry out the visual cycle [14–16].

Aside from the retinoid delivery, IRBP protects retinoids against degradation [17], the retinal cells from oxidative stress and light-induced injury [18, 19], and is important for eye development [20].

## 2. Pathologies associated with IRBP deficiency

In pathological conditions in which a deficiency of IRBP exists, an important anomaly of the photoreceptor cells and the visual cycle can be detected which leads in some cases to the development of retinitis pigmentosa, accumulation of the cytotoxic bis-retinoid A2E, cone-rod photoreceptor dystrophy and an elongated myopic eye shape [20–25].

IRBP is linked to an autosomal recessive form of retinitis pigmentosa. A heterozygous T-C transition at the position 3024 [26] and a missense mutation of D1080N [22] have been identified. *In vitro* studies of this mutation have shown that it produces a non-secreted protein that induces endoplasmic reticular (ER) stress [27].

Other studies correlate the presence of *IRBP* gene mutations and the occurrence of high myopia in humans. This myopia was accompanied with retinal dystrophy observed by ocular coherence tomography (OCT) and electroretinography (ERG). The ERG showed a delay and reduction in the amplitude of the waves corresponding to the cone response. The *IRPB* gene mutations were c.3454G > T;p.E1152 and c.1530 T > A;p.Y510 which were predicted to lead to a nonsense mediated decay with a complete loss of IRBP function [21]. These findings correlate with animal studies in which IRBP<sup>-/-</sup> mice have shown ERG alterations and histological findings affecting cones [25]. This animal model has also shown alterations in eye shape and visual acuity [20].

The relationship between IRBP deficiency and accumulation of the lipofuscin precursor A2E has only been demonstrated experimentally on two different animal models. IRBP<sup>-/-</sup> mice have been shown by HPLC a retinal A2E increase of 2.7-fold [25]. Another study using an animal model with Müller cell dysfunction found a decreased expression of IRBP which was also accompanied with accumulation of A2E [24].

## 3. Diabetes and IRBP levels

Considering visual cycle components, decreased IRBP expression is one of the most characteristic changes in diabetes. Many studies have evaluated the changes in protein levels and IRBP expression and also attempted to explain the reasons for its depletion.

One study revealed decreased expression of IRBP determined by both qPCR and protein quantification on post-mortem samples of diabetic patients [28]. Another study showed that

this decreased expression directly correlated with the evolution of the DR, and also tested the effect of glucose and inflammatory cytokines on IRBP expression *in vitro*. They found that high glucose, TNF- $\alpha$  and IL-1 $\beta$  were able to reduce IRBP's expression [29]. A recent study found decreased IRBP levels in diabetic rats and this finding was accompanied by decreased levels of 11-cRAL and rhodopsin synthesis [30].

The precise mechanisms responsible for the decreased IRBP levels remain unclear. It is known that high glucose and some circulating fatty acids can induce the secretion of inflammatory cytokines by Müller cells [31, 32]. Despite evidence that high levels of glucose and inflammatory cytokines are able to decrease the expression of IRBP [24, 29], other mechanisms may be involved. With the early onset of diabetes, photoreceptors undergo oxidative stress resulting in increased nitrosative-oxidative stress [33, 34]. This biochemical stress can induce damage to proteins promoting their degradation [35]. The unfolded protein response (UPR) has been detected to be active in photoreceptor cells in animal studies [36]; however no studies have linked this process to decreased IRBP levels.

Disruption of the external limiting membrane (ELM) and the outer retinal barrier (ORB) may play a role in leaking of IRBP into the outer nuclear layer or Bruch's membrane. Studies of animals in diabetic conditions have shown decreased occluding abilities in the Müller cell tight junctions compromising the external limiting membrane [37]. Also retinal pigment epithelium (RPE) dysfunction in early stage diabetes has been described in animal models [38]. It is still unclear the impact of these mechanisms over the IRBP levels.

#### 4. Outcomes of IRBP's decreased levels in diabetes

Due to its importance on the visual cycle, it is expected that decreased levels of IRBP produce electrophysiological and morphological changes that manifest itself in the damage to the photoreceptors and the impaired visual cycle.

Deficit of blue-flicker discrimination has been observed in the early stages of diabetes [39]. ERGs have revealed lower oscillatory potential amplitudes suggesting alterations in the photoreceptors and the vision cycle [40–42]. Additionally, color vision has been shown to be altered in these early diabetes stages. Adaptometry studies have also shown alteration in diabetes; even with transient hyperglycemia a patient can have a delay in dark adaptation [43–45].

One study in *Meriones shawi*, an animal model with a human-like macula, after streptozotocin-induced diabetes showed alterations in the morphology of the photoreceptor outer segments. Interestingly, the foveal cones appear to be mostly affected revealing a loss of approximately 30% of the M-cones 7 weeks after type 2 diabetes was induced in the animals [46]. Studies in rats also have shown alterations in the photoreceptor outer segments with the S-cones and the M-cones most severely affected [47].

It has been found that glucose levels can influence the vision cycle rhodopsin regeneration ratio [48, 49]. Recently, one research group found depletion of rhodopsin regeneration with an accompanying decrease in STRA6, IRBP, and 11-cis retinal (11-cRAL) in a diabetic animal model [30].

## 5. Future directions

IRBP deficiency in diabetes could importantly impact DR progression although the relationship between its levels and the complications in diabetes remain unclear. Previous evidence suggest that it potentially impacts DR outcomes. In addition, some retinoid analogues have shown to be beneficial in the prevention of early stage DR due to their antioxidant properties [50, 51]. IRBP has been shown to have these anti-oxidant properties against some vision cycle retinoid sub-products [18].

IRBP deficiency can promote the accumulation of the cytotoxic bis-retinoid A2E. This molecule has been described to be involved in the pathogenesis of age-related macular degeneration (AMD) [52, 53] and Stargardt disease [54]. A2E is known to be able to produce cytotoxicity by destabilizing membranes, generating reactive oxygen species and producing photo-oxidation [55–58]. Since A2E is a lipofuscin precursor, fundus autofluorescence can be clinically used to detect its presence [59, 60]. However, hard exudates can decrease autofluorescence interfering with the evaluation of lipofuscin [61]. It would be expected that this accumulation of lipofuscin precursors in diabetes would increase the risk for developing AMD. Many studies have shown contradictory results and this relationship has not been established [62–65]. The actual accumulation, as well as the role of A2E in diabetes complications, is unclear and require further investigation.

It is important to reveal the mechanisms responsible for decreased IRBP in diabetes and to establish its role in DR in order to establish novel approaches for the prevention of these vision threatening events.

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## References

- [1] Barber AJ, Lieth E, Khin SA, Antonetti DA, Buchanan AG, Gardner TW. Neural apoptosis in the retina during experimental and human diabetes. Early onset and effect of insulin. *Journal of Clinical Investigation*. 1998;**102**:783-791
- [2] Tavares Ferreira J, Alves M, Dias-Santos A, Costa L, Santos BO, Cunha JP, Papoila AL, Abegão Pinto L. Retinal neurodegeneration in diabetic patients without diabetic retinopathy. *Investigative Ophthalmology & Visual Science*. 2016;**57**:6455-6460
- [3] Carrasco E, Hernández C, de Torres I, Farrés J, Simó R. Lowered cortistatin expression is an early event in the human diabetic retina and is associated with apoptosis and glial activation. *Molecular Vision*. 2008;**14**:1496-1502



- [4] Park SH, Park JW, Park SJ, Kim KY, Chung JW, Chun MH, Oh SJ. Apoptotic death of photoreceptors in the streptozotocin-induced diabetic rat retina. *Diabetologia*. 2003;**46**:1260-1268
- [5] Lieth E, Barber AJ, Xu B, Dice C, Ratz MJ, Tanase D, Strother JM. Glial reactivity and impaired glutamate metabolism in short-term experimental diabetic retinopathy. Penn State Retina Research Group. *Diabetes*. 1998;**47**:815-820
- [6] Carter-Dawson L, Burroughs M. Differential distribution of interphotoreceptor retinoid-binding protein (IRBP) around retinal rod and cone photoreceptors. *Current Eye Research*. 1989;**8**:1331-1334
- [7] Anderson DH, Neitz J, Saari JC, Kaska DD, Fenwick J, Jacobs GH, Fisher SK. Retinoid-binding proteins in cone-dominant retinas. *Investigative Ophthalmology & Visual Science*. 1986;**27**:1015-1026
- [8] Schneider BG, Papermaster DS, Liou GI, Fong SL, Bridges CD. Electron microscopic immunocytochemistry of interstitial retinol-binding protein in vertebrate retinas. *Investigative Ophthalmology & Visual Science*. 1986;**27**:679-688
- [9] Gonzalez-Fernandez F, Landers RA, Glazebrook PA, Fong SL, Liou GI, Lam DMK, Bridges CDB. An extracellular retinol-binding glycoprotein in the rat eye—Characterization, localization and biosynthesis. *Neurochemistry International*. 1985;**7**:533-540
- [10] Fong SL, Liou GI, Landers RA, Alvarez RA, Gonzalez-Fernandez F, Glazebrook PA, Lam DMK, Bridges CDB. Characterization, localization, and biosynthesis of an interstitial retinol-binding glycoprotein in the human eye. *Journal of Neurochemistry*. 1984;**42**:1667-1676
- [11] Porrello K, Bhat SP, Bok D. Detection of interphotoreceptor retinoid binding protein (IRBP) mRNA in human and cone-dominant squirrel retinas by in situ hybridization. *Journal of Histochemistry & Cytochemistry*. 1991;**39**:171-176
- [12] Hollyfield JG, Fliesler SJ, Rayborn ME, Fong SL, Landers RA, Bridges CD. Synthesis and secretion of interstitial retinol-binding protein by the human retina. *Investigative Ophthalmology & Visual Science*. 1985;**26**:58-67
- [13] Gonzalez-Fernandez F, Landers RA, Glazebrook PA, Fong SL, Liou GI, Lam DM, Bridges CD. An extracellular retinol-binding glycoprotein in the eyes of mutant rats with retinal dystrophy: Development, localization, and biosynthesis. *The Journal of Cell Biology*. 1984;**99**:2092-2098
- [14] Qtaishat NM, Wiggert B, Pepperberg DR. Interphotoreceptor retinoid-binding protein (IRBP) promotes the release of all-trans retinol from the isolated retina following rhodopsin bleaching illumination. *Experimental Eye Research*. 2005;**81**:455-463
- [15] Betts-Obregon BS, Gonzalez-Fernandez F, Tsin AT. Interphotoreceptor retinoid-binding protein (IRBP) promotes retinol uptake and release by rat Müller cells (rMC-1) in vitro: Implications for the cone visual cycle. *Investigative Ophthalmology & Visual Science*. 2014;**55**:6265-6271
- [16] Carlson A, Bok D. Promotion of the release of 11-cis-retinal from cultured retinal pigment epithelium by interphotoreceptor retinoid-binding protein. *Biochemistry*. 1992;**31**:9056-9062

- [17] Gonzalez-Fernandez F, Betts-Obregon B, Yust B, Mimun J, Sung D, Sardar D, Tsin AT. Interphotoreceptor retinoid-binding protein protects retinoids from photodegradation. *Photochemistry and Photobiology*. 2015;**91**:371-378
- [18] Lee M, Li S, Sato K, Jin M. Interphotoreceptor retinoid-binding protein mitigates cellular oxidative stress and mitochondrial dysfunction induced by all-trans-retinal. *Investigative Ophthalmology & Visual Science*. 2016;**57**:1553-1562
- [19] Sun Z, Zhang M, Liu W, Tian J, Xu G. Photoreceptor IRBP prevents light induced injury. *Frontiers in Bioscience (Landmark Ed)*. 2016;**21**:958-972
- [20] Markand S, Baskin NL, Chakraborty R, Landis E, Wetzstein SA, Donaldson KJ, Priyadarshani P, Alderson SE, Sidhu CS, Boatright JH, Iuvone PM, Pardue MT, Nickerson JM. IRBP deficiency permits precocious ocular development and myopia. *Molecular Vision*. 2016;**22**:1291-1308
- [21] Arno G, Hull S, Robson AG, Holder GE, Cheetham ME, Webster AR, Plagnol V, Moore AT. Lack of interphotoreceptor retinoid binding protein caused by homozygous mutation of RBP3 is associated with high myopia and retinal dystrophy. *Investigative Ophthalmology & Visual Science*. 2015;**56**:2358-2365
- [22] den Hollander AI, McGee TL, Ziviello C, Banfi S, Dryja TP, Gonzalez-Fernandez F, Ghosh D, Berson EL. A homozygous missense mutation in the IRBP gene (RBP3) associated with autosomal recessive retinitis pigmentosa. *Investigative Ophthalmology & Visual Science*. 2009;**50**:1864-1872
- [23] Wisard J, Faulkner A, Chrenek MA, Waxweiler T, Waxweiler W, Donmoyer C, Liou GI, Craft CM, Schmid GF, Boatright JH, Pardue MT, Nickerson JM. Exaggerated eye growth in IRBP-deficient mice in early development. *Investigative Ophthalmology & Visual Science*. 2011;**52**:5804-5811
- [24] Zhu L, Shen W, Lyons B, Wang Y, Zhou F, Gillies MC. Dysregulation of inter-photoreceptor retinoid-binding protein (IRBP) after induced Müller cell disruption. *Journal of Neurochemistry*. 2015;**133**:909-918
- [25] Jin M, Li S, Nusinowitz S, Lloyd M, Hu J, Radu RA, Bok D, Travis GH. The role of interphotoreceptor retinoid-binding protein on the translocation of visual retinoids and function of cone photoreceptors. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*. 2009;**29**:1486-1495
- [26] Valverde D, Vázquez-Gundín F, dR E, Calaf M, Fernández JL, Baiget M. Analysis of the IRBP gene as a cause of RP in 45 ARRP Spanish families. Autosomal recessive retinitis pigmentosa. Interstitial retinol binding protein. Spanish Multicentric and Multidisciplinary Group for Research into Retinitis Pigmentosa. *Ophthalmic Genetics*. 1998;**19**:197-202
- [27] Li S, Yang Z, Hu J, Gordon WC, Bazan NG, Haas AL, Bok D, Jin M. Secretory defect and cytotoxicity: The potential disease mechanisms for the retinitis pigmentosa (rp)-associated interphotoreceptor retinoid-binding protein (IRBP). *The Journal of Biological Chemistry*. 2013;**288**:11395-11406

- [28] García-Ramírez M, Canals F, Hernández C, Colomé N, Ferrer C, Carrasco E, García-Arumí J, Simó R. Proteomic analysis of human vitreous fluid by fluorescence-based difference gel electrophoresis (DIGE): A new strategy for identifying potential candidates in the pathogenesis of proliferative diabetic retinopathy. *Diabetologia*. 2007;**50**:1294-1303
- [29] Garcia-Ramírez M, Hernández C, Villarroel M, Canals F, Alonso MA, Fortuny R, Masmiquel L, Navarro A, García-Arumí J, Simó R. Interphotoreceptor retinoid-binding protein (IRBP) is downregulated at early stages of diabetic retinopathy. *Diabetologia*. 2009;**52**:2633-2641
- [30] Malechka VV, Moiseyev G, Takahashi Y, Shin Y, Ma J-X. Impaired rhodopsin generation in the rat model of diabetic retinopathy. *The American Journal of Pathology*. 2017;**187**:2222-2231
- [31] Capozzi ME, McCollum GW, Cousins DB, Penn JS. Linoleic acid is a diabetes-relevant stimulator of retinal inflammation in human retinal Muller cells and microvascular endothelial cells. *Journal of Diabetes & Metabolism*. 2016;**7**:718
- [32] Liu L, Zuo Z, Lu S, Liu A, Liu X. Naringin attenuates diabetic retinopathy by inhibiting inflammation, oxidative stress and NF- $\kappa$ B activation in vivo and in vitro. *The Iranian Journal of Basic Medical Sciences*. 2017;**20**:813-821
- [33] Aboualizadeh E, Ranji M, Sorenson CM, Sepehr R, Sheibani N, Hirschmugl CJ. Retinal oxidative stress at the onset of diabetes determined by synchrotron FTIR widefield imaging: Towards diabetes pathogenesis. *The Analyst*. 2017;**142**:1061-1072
- [34] Hernández-Ramírez E, Sánchez-Chávez G, Estrella-Salazar LA, Salceda R. Nitrosative stress in the rat retina at the onset of streptozotocin-induced diabetes. *Cellular Physiology and Biochemistry*. 2017;**42**:2353-2363
- [35] Grune T, Reinheckel T, Joshi M, Davies KJ, Proteolysis in cultured liver epithelial cells during oxidative stress role of the multicatalytic proteinase complex, proteasome. *The Journal of Biological Chemistry*. 1995;**270**:2344-2351
- [36] Shruthi K, Reddy SS, Reddy GB. Ubiquitin-proteasome system and ER stress in the retina of diabetic rats. *Archives of Biochemistry and Biophysics*. 2017;**627**:10-20
- [37] Omri S, Omri B, Savoldelli M, Jonet L, Thillaye-Goldenberg B, Thuret G, Gain P, Jeanny JC, Crisanti P, Behar-Cohen F. The outer limiting membrane (OLM) revisited: Clinical implications. *Clinical Ophthalmology (Auckland, N.Z.)*. 2010;**4**:183-195
- [38] Samuels IS, Bell BA, Pereira A, Saxon J, Peachey NS. Early retinal pigment epithelium dysfunction is concomitant with hyperglycemia in mouse models of type 1 and type 2 diabetes. *Journal of Neurophysiology*. 2015;**113**:1085-1099
- [39] Daley ML, Watzke RC, Riddle MC. Early loss of blue-sensitive color vision in patients with type I diabetes. *Diabetes Care*. 1987;**10**:777-781
- [40] Bresnick GH, Palta M. Predicting progression to severe proliferative diabetic retinopathy. *Archives of Ophthalmology*. 1987;**105**:810-814



- [41] Juen S, Kieselbach GF. Electrophysiological changes in juvenile diabetics without retinopathy. *Archives of Ophthalmology*. 1990;**108**:372-375
- [42] Yamamoto S, Kamiyama M, Nitta K, Yamada T, Hayasaka S. Selective reduction of the S cone electroretinogram in diabetes. *British Journal of Ophthalmology*. 1996;**80**:973-975
- [43] Greenstein V, Sarter B, Hood D, Noble K, Carr R. Hue discrimination and S cone pathway sensitivity in early diabetic retinopathy. *Investigative Ophthalmology & Visual Science*. 1990;**31**:1008-1014
- [44] Tan NC, Yip WF, Kallakuri S, Sankari U, Koh YLE. Factors associated with impaired color vision without retinopathy amongst people with type 2 diabetes mellitus: A cross-sectional study. *BMC Endocrine Disorders*. 2017;**17**:29
- [45] Holfort SK, Jackson GR, Larsen M. Dark adaptation during transient hyperglycemia in type 2 diabetes. *Experimental Eye Research*. 2010;**91**:710-714
- [46] Hammoum I, Benlarbi M, Dellaa A, Szabó K, Dékány B, Csaba D, Almási Z, Hajdú RI, Azaiz R, Charfeddine R, Lukáts Á, Ben Chaouacha-Chekir R. Study of retinal neurodegeneration and maculopathy in diabetic Meriones shawi: A particular animal model with human-like macula. *Journal of Comparative Neurology*. 2017;**525**:2890-2914
- [47] Énzsöly A, Szabó A, Kántor O, Dávid C, Szalay P, Szabó K, Szél Á, Németh J, Lukáts Á. Pathologic alterations of the outer retina in streptozotocin-induced diabetes. *Investigative Ophthalmology & Visual Science*. 2014;**55**:3686-3699
- [48] Ostroy SE, Frede SM, Wagner EF, Gaitatzes CG, Janle EM. Decreased rhodopsin regeneration in diabetic mouse eyes. *Investigative Ophthalmology & Visual Science*. 1994;**35**:3905-3909
- [49] Ostroy SE, Friedmann AL, Gaitatzes CG. Extracellular glucose dependence of rhodopsin regeneration in the excised mouse eye. *Experimental Eye Research*. 1992;**55**:419-423
- [50] Berkowitz BA, Kern TS, Bissig D, Patel P, Bhatia A, Kefalov VJ, Roberts R. Systemic retinaldehyde treatment corrects retinal oxidative stress, rod dysfunction, and impaired visual performance in diabetic mice. *Investigative Ophthalmology & Visual Science*. 2015;**56**:6294-6303
- [51] Liu H, Tang J, Du Y, Lee CA, Golczak M, Muthusamy A, Antonetti DA, Veenstra AA, Amengual J, von Lintig J, Palczewski K, Kern TS. Retinylamine benefits early diabetic retinopathy in mice. *The Journal of Biological Chemistry*. 2015;**290**:21568-21579
- [52] Ueda K, Zhao J, Kim HJ, Sparrow JR. Photodegradation of retinal bisretinoids in mouse models and implications for macular degeneration. *Proceedings of the National Academy of Sciences of the United States of America*. 2016;**113**:6904-6909
- [53] Wu Y, Yanase E, Feng X, Siegel MM, Sparrow JR. Structural characterization of bisretinoid A2E photocleavage products and implications for age-related macular degeneration. *Proceedings of the National Academy of Sciences of the United States of America*. 2010;**107**:7275-7280

- [54] Weng J, Mata NL, Azarian SM, Tzekov RT, Birch DG, Travis GH. Insights into the function of rim protein in photoreceptors and etiology of Stargardt's disease from the phenotype in abcr knockout mice. *Cell*. 1999;**98**:13-23
- [55] Sparrow JR, Parish CA, Hashimoto M, Nakanishi K. A2E, a lipofuscin fluorophore, in human retinal pigmented epithelial cells in culture. *Investigative Ophthalmology & Visual Science*. 1999;**40**:2988-2995
- [56] De S, Sakmar TP. Interaction of A2E with model membranes. Implications to the pathogenesis of age-related macular degeneration. *The Journal of General Physiology*. 2002;**120**:147-157
- [57] Ben-Shabat S, Itagaki Y, Jockusch S, Sparrow JR, Turro NJ, Nakanishi K. Formation of a nonaoxirane from A2E, a lipofuscin fluorophore related to macular degeneration, and evidence of singlet oxygen involvement. *Angewandte Chemie (International Ed. in English)*. 2002;**41**:814-817
- [58] Rózanowska M, Jarvis-Evans J, Korytowski W, Boulton ME, Burke JM, Sarna T. Blue light-induced reactivity of retinal age pigment. In vitro generation of oxygen-reactive species. *The Journal of Biological Chemistry*. 1995;**270**:18825-18830
- [59] Yung M, Klufas MA, Sarraf D. Clinical applications of fundus autofluorescence in retinal disease. *International Journal of Retina and Vitreous*. 2016;**2**:12
- [60] Venkatesh P, Sagar P, Chawla R, Gogia V, Vohra R, Sharma YR. Evaluation of fundus autofluorescence patterns in age-related macular degeneration. *International Journal of Ophthalmology*. 2016;**9**:1779-1784
- [61] Calvo-Maroto AM, Perez-Cambrodi RJ, Garcia-Lazaro S, Ferrer-Blasco T, Cerviño A. Ocular autofluorescence in diabetes mellitus. A review. *Journal of Diabetes*. 2016;**8**:619-628
- [62] Leske MC, SY W, Hennis A, Nemesure B, Yang L, Hyman L, Schachat AP. Nine-year incidence of age-related macular degeneration in the Barbados Eye Studies. *Ophthalmology*. 2006;**113**:29-35
- [63] Tan JS, Mitchell P, Smith W, Wang JJ. Cardiovascular risk factors and the long-term incidence of age-related macular degeneration: The Blue Mountains Eye Study. *Ophthalmology*. 2007;**114**:1143-1150
- [64] Delcourt C, Michel F, Colvez A, Lacroux A, Delage M, Vernet MH. Associations of cardiovascular disease and its risk factors with age-related macular degeneration: The POLA study. *Ophthalmic Epidemiology*. 2001;**8**(4):237-249
- [65] Fraser-Bell S, Wu J, Klein R, Azen SP, Hooper C, Foong AW, Varma R. Cardiovascular risk factors and age-related macular degeneration: The Los Angeles Latino Eye Study. *American Journal of Ophthalmology*. 2008;**145**:308-316

